Impact of paediatric onset primary sclerosing cholangitis on clinical course and outcome of inflammatory bowel disease : a case-control population-based study in Finland

Tenca, Andrea

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TITLE: Impact of Paediatric Onset Primary Sclerosing Cholangitis on Clinical Course and Outcome of Inflammatory Bowel Disease: a Case-Control Population-Based Study in Finland

SHORT-TITLE: PSC and Paediatric IBD

AUTHORS: Andrea Tenca, MD, PhD[1], Tytti Jaakkola, MD[2], Martti Färkkilä, MD, PhD[1], Johanna Arola, MD, PhD[3], Kaija-Leena Kolho, MD, PhD[2,4]

AFFILIATIONS: [1]University of Helsinki and Helsinki University Hospital/Clinic of Gastroenterology, Helsinki, Finland. [2]University of Helsinki and Children's Hospital/Department of Pediatric Gastroenterology, Helsinki, Finland. [3]Helsinki University and Helsinki University Hospital/Department of Pathology, Helsinki, Finland [4]University of Tampere and Tampere University Hospital

CORRESPONDING AUTHOR: Andrea Tenca, Clinic of Gastroenterology, Department of Medicine, Helsinki University Hospital and University of Helsinki, POB 340, 00029 HUS, Helsinki, Finland. Phone number: +358-09 471 74119. Fax number: +358-09 471 74688. E-mail: ante14@hotmail.it

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ABSTRACT

INTRODUCTION AND AIM

The aim of this study was to investigate the outcome of a paediatric onset of inflammatory bowel disease (IBD) in a cohort of subjects with primary sclerosing cholangitis (PSC) and in a matched-age population-based control group without PSC.

METHODS

We identified 28 IBD-PSC cases (median age at IBD diagnosis 12.5 years, 25-75th: 10-16 years) and selected three IBD controls for each case matched for age and year of IBD diagnosis. All data regarding the gastrointestinal tract and liver were collected at diagnosis and at last follow-up (median 15 years).

RESULTS

At diagnosis the prevalence of pancolitis was similar between the groups (78% and 79%, respectively p= 0.30), but histologic inflammation was milder in IBD-PSC (61% vs 30%, p= 0.06). At last follow-up (median age 29 years) pancolitis was less frequent (6% and 33%, respectively p=0.04) and the remission higher (76% and 47%, respectively p=0.08) in IBD-PSC patients than in IBD patients. Panproctolectomy (32% in IBD-PSC and 34% in IBD, p=1.0) and the rate of pouchitis (62% and 70%, respectively p= 0.8) were similar.

CONCLUSIONS

The outcome of paediatric onset IBD in patients with PSC in adulthood seems to be comparable to those with IBD only.

KEY WORDS: primary sclerosing cholangitis; autoimmune liver disease; dysplasia; colorectal cancer; pouchitis; ulcerative colitis

ABBREVIATIONS

Primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), primary sclerosing cholangitis/autoimmune hepatitis overlap syndrome (PSC/AIH), autoimmune sclerosing cholangitis (ASC), inflammatory bowel diseases (IBD), ulcerative colitis (UC), Crohn's disease (CD), unclassified colitis (IBD-U), 5-aminosalicylic acid (5-ASA), tumour necrosis factor (TNF)-alfa inhibitors, Helsinki University Hospital (HUH), international autoimmune hepatitis group (IAIHG).

INTRODUCTION

Primary sclerosing cholangitis (PSC) is an inflammatory and fibrotic disease characterised by strictures and dilatations, involving both the intra- and extra-hepatic bile ducts [1].

The disease affects mostly males around the age of 34-40 years [1], but it may also occur in children. In childhood, 30-50% of patients present a unique phenotype characterised by an overlap with autoimmune hepatitis (AIH), i.e., elevation of transaminases, positive autoantibodies, interface hepatitis in liver biopsy, and they are so referred to as having autoimmune sclerosing cholangitis (ASC) or PSC-AIH overlap syndrome [2].

The aetiology of PSC in children and in adults is unknown, but an interaction between a genetic predisposition [3-5] and environmental factors [6] has been proposed. The disease is associated in the majority of the patients with inflammatory bowel disease (IBD), with ulcerative colitis (UC) being the most common form and less frequently Crohn´s disease (CD) and unclassified-colitis (IBD-U) [7]. In adults IBD associated with PSC (IBD-PSC) might present a different genetic profile [8]. Still, IBD-PSC presents a unique phenotype, characterised by mild inflammation, rectal sparing, backwash ileitis and a higher risk of colon-rectal cancer. [9]. However, data on the clinical course and prognosis of IBD in patients with a paediatric onset IBD-PSC are underreported and conflicting (Supplement 1).

Thus, this study was aimed at comparing the clinical course and follow-up of IBD in a cohort of patients with a paediatric onset of IBD-PSC and in a population-based group of patients with a paediatric onset of IBD only.

METHODS

Study design

This is an observational longitudinal retrospective case-control population-based study.

Study area, population and time.

Helsinki University Hospital (HUH) is a Tertiary Referral Centre in Finland (overall population about 5.6 million inhabitants), serving a defined population of about 1.5 million inhabitants and covering approximately 30% of the total child population in the country (www.stat.fi). Most paediatric and adult patients with PSC are referred from all over the country to this centre for diagnosis and the follow-up of the disease.

We identified 28 patients with a diagnosis of IBD-PSC in childhood or during adolescence (≤ 20 years; diagnosed between 1989 and 2011) [10].

For each IBD-PSC case, three IBD controls matched for age and year of IBD diagnosis were selected from the IBD Study Registry at HUH. Since the majority of children with PSC presented with UC or IBD-U (26/28, 93%) and the two patients with CD had pancolitis, only controls with UC/IBD-U were selected.

PSC-ascertainment

All medical records were reviewed to ensure the correct diagnosis.

Diagnosis of PSC was based on: 1. elevation of liver enzymes (i.e., gamma glutamyltranspeptidase and/or alkaline phosphatase and alanine aminotransferase), 2. typical cholangiographic features of the disease (i.e., strictures and dilations involving both intra- and/or extra-hepatic bile ducts) obtained by endoscopic retrograde cholangiography (ERC), 3. histologic features in the liver biopsy compatible with PSC or PSC-AIH and 4. other imaging techniques suggestive of PSC (i.e., magnetic resonance imaging). In this respect, all liver biopsies were reviewed by an experienced pathologist blinded for the patients' outcome. Patients fulfilling the diagnostic criteria for both PSC and AIH [10] were diagnosed as having PSC-AIH; the modified diagnostic score for AIH proposed by the IAIHG in 1999 [11] was retrospectively applied to the patients to ensure the diagnosis of PSC-AIH [10].

Patients affected by secondary sclerosing cholangitis, as well as by other liver diseases (i.e., genetic, viral and/or metabolic), were excluded.

IBD-ascertainment

The disease extent at diagnosis of IBD and at the last follow-up were reviewed according to the Paris Classification of Ulcerative Colitis criteria [12]. In detail, disease extent (i.e., E1: distal proctitis, E2: left-sided colitis, E3: extensive colitis, E4: pancolitis) and severity (i.e., S0: Prednisolone/Prednisone never used and S1: Prednisolone/Prednisone used at least once during the follow-up) were collected. Similarly, the following histological features in colonoscopy were collected: location of inflammation, the type of inflammation (absence/inactive or active), the degree of active inflammation (i.e., mild, moderate, severe) and the localisation and degree (i.e., mild or severe) of dysplasia.

Medications (i.e., glucorticosteroids, 5-aminosalicylic acid or 5-ASA, thiopurine, TNF-alfa inhibitors) and surgery (i.e., time and type of surgery and eventually any complications such as pouchitis) were also collected.

Follow-up

For the study purpose, follow-up was considered to start when the patient was referred to HUH for the diagnosis of IBD and ended by the index date 01.09.2018.

Statistical analysis

Data are presented as number with percentage when categorical and as median with 25-75 percentiles when continuous. Differences were tested by using Fisher´s Exact Test or the Chi-Square Test for categorical and Mann-Whitney Test for continuous variables. p was considered statistically significant when < 0.05.

Ethics

The study was approved by the Ethics Committee of HUH (number 64/13/03/03/2012).

RESULTS

Baseline characteristics of IBD-PSC cases and IBD-controls.

Twenty-eight IBD-PSC patients (birth dates between 1976-2001) with a median age at IBD diagnosis of 12.5 years and median age at PSC diagnosis of 15 years were included. Eighteen children (64%) had PSC, and 10 (36%) were PSC-AIH; no cases of isolated small duct PSC were seen. Eighty-four matched IBD-controls were eligible (median age at IBD diagnosis 12 years) (Table 1). Baseline characteristics of PSC cases with and without AIH are reported in Supplement 2.

Last follow-up

The median length of follow-up was 14 years (25-75th: 10.0-19.7) in the IBD-PSC group and 15 years (25-75th: 11.0-19.0) in the IBD-controls. At the end of follow-up, the median age was 29.0 years in the IBD-PSC group (25-75th: 22.5-33.7) and 28.0 years (25-75th: 23-31.0) in the IBD controls. We found no statistically significant differences between the two groups (Table 1). Baseline characteristics of PSC cases with and without AIH are reported in Supplement 2.

Endoscopic location of IBD and disease severity at diagnosis and last follow-up according to the Paris Classification Criteria.

Data concerning disease extent and severity in IBD-PSC cases and IBD-controls are summarised in Table 2.

We did not find any statistically significant difference in endoscopic disease extent at IBD diagnosis (p= 0.30). At diagnosis, most patients had pancolitis (IBD-PSC 78% and IBD 79%). Backwash ileitis was detected in two patients with IBD-PSC and in two with IBD respectively, and rectal sparing was seen in one patient with IBD-PSC.

However, at the last follow-up the endoscopic remission rate was higher in the IBD-PSC than in the IBD-control group (75% vs 47%), the difference being close to statistical significance (p= 0.08) (Figure 1). Pancolitis (i.e. E4) was more frequent in the IBD-control than in the IBD-PSC group (33% vs. 6 %; p= 0.04).

Histological inflammation at diagnosis and last follow-up.

Data on histological findings are summarised in Table 3. All the patients had active colitis at diagnosis. Three IBD-PSC cases also had inflammation in the terminal ileum and one in the colon with rectal sparing. Among IBD-cases, inflammation involved the rectum only in 3, the left-side in 4, up to the hepatic flexure in 4; ten patients also had inflammation in the terminal ileum. We found a statistically significant difference in the degree of histologic inflammation at time of diagnosis between IBD-PSC cases and IBD controls, with IBD-PSC patients having more frequently inflammation graded as mild (61% vs 30%, p= 0.006) (Figure 2) and IBD patients more frequently graded as severe (35% vs 8%, p= 0.006). No cases of dysplasia or cancer were detected at IBD diagnosis.

We did not find any statistically significant difference between IBD-PSC cases and IBD-controls for the presence and degree of inflammation at the last follow-up, although inflammation tended to be graded more frequently as mild among IBD-PSC cases (62 vs 31%, p= 0.08).

One 26-year old IBD-PSC patient developed low-grade dysplasia in the colon and underwent a panproctocolectomy with a J-pouch. We found no cases of adenocarcinoma in the colon.

Medical treatment during the follow-up and at last follow-up

During follow-up, 5 IBD-PSC patients (classified as PSC-AIH) had used glucocorticosteroids and thiopurine for their liver disease. The other patients on these drugs had their intestinal disease as an indication (Supplement 3). IBD controls had more frequently used glucocortiosteroids at least once than the IBD-PSC group (84% vs 64%, p=0.03). Still, the number of IBD-controls on TNF-alpha inhibitors during follow-up was higher, although not statistically significant (28% vs 14%, p=0.20). We found a statistically significant difference in disease severity (overall use of glucocorticosteroids) at the last follow-up between IBD-PSC cases and IBD-controls (p= 0.03) (Supplement 3).

Surgery during follow-up.

Data on surgery are summarised in Supplement 4 and 5. We found no statistically significant difference in the number of panprocto-colectomies between IBD-PSC cases (9/28; 32%) and IBD-controls (31/84; 34%, p=1.0). Among IBD-PSC cases, a J-pouch was performed in eight 8/9 (89%)

and ileostomy in one. Among IBD-controls, a J-pouch was performed in 27 (87%), but in two cases, it was followed by ileostomy because of severe pouchitis; ileostomy was performed as first treatment in two. The rate of pouchitis (5/8, 62% vs 19/27, 70%, p= 0.8) and recurrent pouchitis (4/5, 80% vs 15/19, 79%, p= 1.0) was similar between the groups. Twenty-four IBD-PSC patients (86%) received repeatedly metronidazole for prevention of cholangitis. The 19 IBD controls with pouchitis received metronidazole and/or ciprofloxacin, one patient received stool transplantation and two were operated on with ileostomy. Among IBD-PSC cases, extra-intestinal surgery was performed in four: two patients underwent liver transplantation (repeatedly confirmed dysplasia and aneuploidy in one and progressive increment of Ca 19-9 with cirrhosis in one), one splenectomy for autoimmune thrombocytopenia and one cholecystectomy for lithiasis.

DISCUSSION

Statement of principal findings. The clinical course and outcome of IBD in children with PSC is underreported in the literature [13]. To our knowledge, this is the first case-control population-based study in Europe reporting a long-term follow-up (median 15 years) until adulthood of a paediatric onset IBD between two groups of patients, i.e., with and without PSC.

The main findings of this study are: 1. At diagnosis, children with IBD-PSC and IBD had comparable disease extent (i.e., mostly pancolitis), but patients with IBD-PSC were more often in remission and had less pancolitis after a median follow-up of 15 years, 2. At diagnosis and during follow-up IBD-PSC children had mild histological inflammation, 3. Colon dysplasia was detected in one patient with IBD-PSC, 4. Medical treatment and need for surgery were comparable between children with IBD-PSC and IBD 5. IBD-PSC patients with a J-pouch had the same rate of pouchitis than patients with IBD.

Disease location and severity. IBD-PSC and PSC patients had the same rate of pancolitis at diagnosis, which is in contrast with the current literature. However, IBD-PSC patients tended to have a higher remission rate and less pancolitis than IBD patients at a median follow-up of 15 years.

A recent meta-analysis in children has reported an association between IBD-PSC and pancolitis (RR 1.42; 95%CI: 1.22-1.64) [13]. At diagnosis of IBD, Ordonez et al. has found a higher rate of pancolitis in children with IBD also associated with autoimmune disease other than PSC (i.e., PSC-AIH, AIH, coeliac disease and hypereosinophilic syndrome) [14]. Lascurain et al. and Shiau et al. reported that pancolitis was more common in children with IBD-PSC then in those with only IBD (90% vs 72% and 96% vs 64%, respectively) [15, 16]. The same meta-analysis has shown an association between IBD-PSC and rectal sparing (RR 3.91; 95%CI: 1.31-11.62), but not with backwash ileitis (RR 2.43; 95%CI: 0.86-6.89). In adults, IBD-PSC may present a unique phenotype characterised by mild inflammation with a right side predominance and a pancolonic involvement associated to backwash ileitis and a rectal sparing [9]. In our study, backwash ileitis and rectal sparing were rare. This is in line with previous reports as rectal sparing has been detected in only 7-26% of the children, querying the "unique IBD phenotype" in the paediatric population [14, 15, 17].

Histology and dysplasia. In IBD-PSC children, inflammation was mostly mild at diagnosis and at the last follow-up. To our knowledge, this is the first population-based study comparing histologic characteristics of intestinal inflammation between children with IBD-PSC and only IBD. A similar result was reported in adults [18]. In a retrospective series, Faubion et al. found a mild-moderate degree of inflammation in 83% of children with IBD-PSC [17], which is similar to our rate of 92%. Recently, Ricciuto et al. has shown in a prospective study including 87 children with colitis that children with PSC in clinical remission have more subclinical inflammation that in turn might play a role in the development of colorectal cancer [19]. PSC is a risk factor for colorectal cancer in IBD. In a Dutch population-based study, patients with IBD-PSC had a 10-fold increased risk of colon-rectal cancer compare to UC-controls [20]. However, the risk in a paediatric onset IBD-PSC is still unclear. None of the studies on the clinical course and prognosis of a paediatric onset PSC [10, 21-25] reported any case of colorectal cancer/dysplasia during a median follow-up of 4-9 years. Among the studies conducted on the clinical course and prognosis of a paediatric onset IBD-PSC [14-17], only Faubion et al reported three cases of dysplasia in the colon (17, 23, 32-year-olds at 4 months, 10 years and 22 years after IBD

diagnosis) [17]. In our study, one patient with IBD-PSC developed low-grade dysplasia at the age of 26 years, after 10 years from IBD diagnosis. In our centre, all PSC patients receive ursodeoxycholic acid at low dosage (15 mg/Kg), which in some studies has been reported to reduce the inflammation in the colon [26] and the risk of colon cancer in patients with IBD-PSC [27]. However, this result needs what the current guidelines recommend - to perform a screening ileocolonscopy at the time of PSC diagnosis and then every year in patients with IBD-PSC [28, 29]. However, the right policy is still unclear in children and adolescents, since ileocolonscopy is an invasive procedure, needing deep sedation. Further multi-centre prospective studies are needed in the future to fill this important gap. However, we believe that annual colonoscopies are not needed in young children when in remission (i.e. low fecal calprotectin) as ongoing inflammation is the major risk factor for adenocarcinoma [30, 31]. In the above-mentioned study, Ricciuto et al also showed that fecal calprotectin with a value < 100 mcg/g performed better than the symptom-based clinical activity index in detecting mucosal healing in children with IBD-PSC [19].

Medical treatment. During the follow-up, patients with IBD had more frequently used glucocorticosteroids. This finding might suggest a more benign course of IBD in patients with IBD-PSC. Turunen et al has reported a more aggressive course of IBD in children then in adults with about 80% of the paediatric patients needing glucocorticoids at some point of the follow-up [32]. Shiau et al. found less use of steroids and TNF-alfa inhibitors in children with IBD-PSC [16]. However, we did not find any difference in the use of 5-ASA compounds, thiopurine and TNF-alfa inhibitors. Notably, it is challenging to draw conclusions on the effect of medical treatment in patients with IBD-PSC, since many of them have an overlap with AIH, hampering the assessment of indications in a retrospective study to differentiate whether the glucocorticoids/immunosuppressors were used for liver disease or for intestinal disease.

Surgical treatment. During the follow-up, patients with IBD-PSC and IBD had similar numbers of panproctolecotmies with J-pouch reconstructions; ileostomy was seldom performed in both groups. Lascurain et al. reported a higher number of colectomies in IBD-PSC patients than in IBD-controls,

although the difference was not statistically significant [15]. The same study group has also reported autoimmune liver disease as a risk factor for colectomy [15], however, this was not the case in our study, although we had a similar rate of AIH overlap syndrome study (36% vs 33%) and a longer follow-up.

Pouchitis is a frequent finding, and the rates of pouchitis and recurrent pouchitis were similar in patients with IBD-PSC and IBD during the median 12-year follow-up after surgery. Faubion et al reported at least one episode of pouchitis in four out of five patients with a paediatric onset IBD-PSC after 1.5 year from colectomy [17]. Lascurain et al more recently reported that the rate of pouchitis was 100% in IBD-PSC group and 64% in IBD-controls at 5 year follow-up [15]. Penna et al. has reported a higher rate of pouchitis after colectomy and pouch-anal anastomosis in adult patients with IBD-PSC [33]. The majority of the IBD-PSC patients in our study received metronidazole since, as previously reported, metronidazole with ursodeoxycholic acid improve alkaline phosphatase level and Mayo score in patients with PSC [34]. We speculate that the cyclic use of metronidazole might affect the risk of pouchitis in patients with IBD-PSC, but further multi-centre prospective studies are needed in the future to investigate the risk of pouchitis in larger cohorts of patients with paediatric onset IBD-PSC.

Conclusions. The phenotypes of IBD in children and adolescents with IBD-PSC and IBD only are indistinguishable at diagnosis as both mostly present as pancolitis. Patients with IBD-PSC seem to have milder histological inflammation, need treatment with glucocorticoids less frequently and achieve remission more often during 15-years follow-up. The need for surgery and rate of pouchitis, however, is similar between patients with a paediatric onset IBD-PSC and IBD. Taken together, these findings suggest a comparable course of IBD in children with IBD-PSC. However, colon dysplasia may occur, necessitating surveillance of inflammation along the disease course, but to define the optimal surveillance protocols, further studies are warranted.

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TABLES

Table 1. Baseline characteristics of IBD-PSC cases and IBD-controls.

	IBD-PSC cases	IBD controls	p
Number	28	84	-
PSC-AIH	10 (36%)	-	-
Males	19 (68%)	39 (46%)	0.06
Median age and 25-75th percentiles at IBD diagnosis in years	12.5, 10-16	12, 10-15	0.4
Median age and 25-75th percentiles at PSC diagnosis in years	15, 12-17	-	-
Median age and 25-75th percentiles at last follow-up in years	29, 22-34	28, 23-31	0.4
Median follow-up duration and 25-75th percentiles in years	14, 10-19.7	15, 11-19	0.8

PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease. AIH: autoimmune hepatitis. p significant < 0.05. For comparisons Fisher' Exact Test and Mann-Whitney Test were used when appropriate.

Table 2. Endoscopic location of IBD and disease severity at diagnosis and last-follow-up in IBD-PSC cases and IBD-controls according to the Paris Classification of Ulcerative Colitis criteria (12).

	At diagnosis		At last follow-up	
	IBD-PSC N=28	**IBD-controls N=84**	**IBD-PSC N=28**	**IBD-controls N=84**
Extent of disease				
Not available	1/28 (4%)	1/84 (1%)	4/28 (14%)	6/84 (7%)
J-pouch surgery/ileostomy	-	-	8/28 (28%)	29/84 (34%)
Normal	2/27 (7%)	1/83 (1%)	12/16 (76%)	23/49 (47%)§
E1	0/27 (0%)	4/83 (5%)	1/16 (6%)	7/49 (14%)
E2	3/27 (11%)	6/83 (7%)	2/16 (12%)	2/49 (4%)
E3	1/27 (4%)	6/83 (7%)	0/16 (0%)	1/49 (2%)
E4	21/27 (78%)	66/83 (79%)	1/16 (6%)	16/49 (33%)*
Severity of disease				
Not available	-	-	0 (0%)	2 (1%)
S0	-	-	10/28 (36%)	13/83 (16%)
S1	-	-	18/28 (64%)*	69/83 (83%)*

PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease.

E1: distal proctitis, E2: left-sided colitis, E3: extensive colitis, E4: pancolitis.

S0: Prednisolone/Prednisone never used, S1: Prednisolone/Prednisone used at least once during the follow-up.

§p= 0.08, *p < 0.05. Fisher Exact Test and global Chi-Square Test were used when appropriate.

Table 3. Histological inflammation at diagnosis and last-follow-up in IBD-PSC cases and IBD-controls.

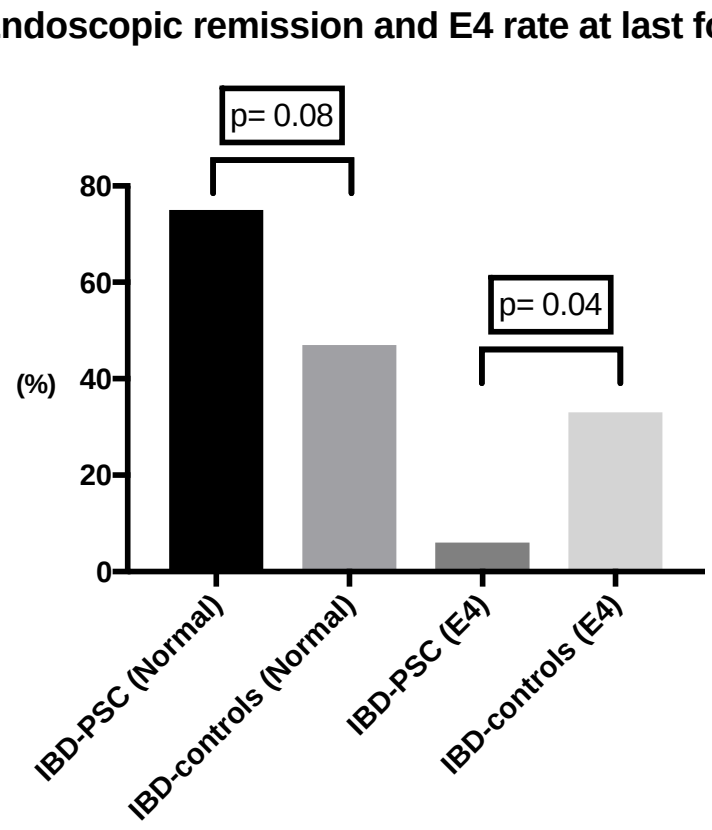
	At diagnosis		At last follow-up	
	IBD-PSC N=28	**IBD-controls N=84**	**IBD-PSC N=28**	**IBD-controls N=84**
Not available	2/28 (7%)	2/84 (2%)	3/28 (11%)	3/84 (4%)
J-pouch surgery/ileostomy	-	-	8/28 (28%)	29/84 (34%)
Absence/Inactive colitis	0 (%)	0 (%)	10/17 (59%)	23/52 (44%)
Active colitis	26 (100%)	82 (100%)	7/17 (41%)	29/52 (56%)
- **Mild**	16/26 (61%)*	25/82 (30%)*	5/7 (62%)	9/29 (31%)§
- **Moderate**	8/26 (31%)	28/82 (34%)	2/7 (38%)	11/29 (38%)
- **Severe**	2/26 (8%)*	29/82 (36%)*	0/7 (0%)	9/29 (31%)°
Dysplasia (mild)	0/28 (0%)	0/82 (0%)	1/17 (6%)	0/52 (0%)
Adenocarcinoma	0/28 (0%)	0/82 (0%)	0/17 (0%)	0/52 (0%)

PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease.

*$p < 0.05$, §$p= 0.08$, °$p= 0.15$. Fisher Exact Test and global Chi-Square Test were used when appropriate.

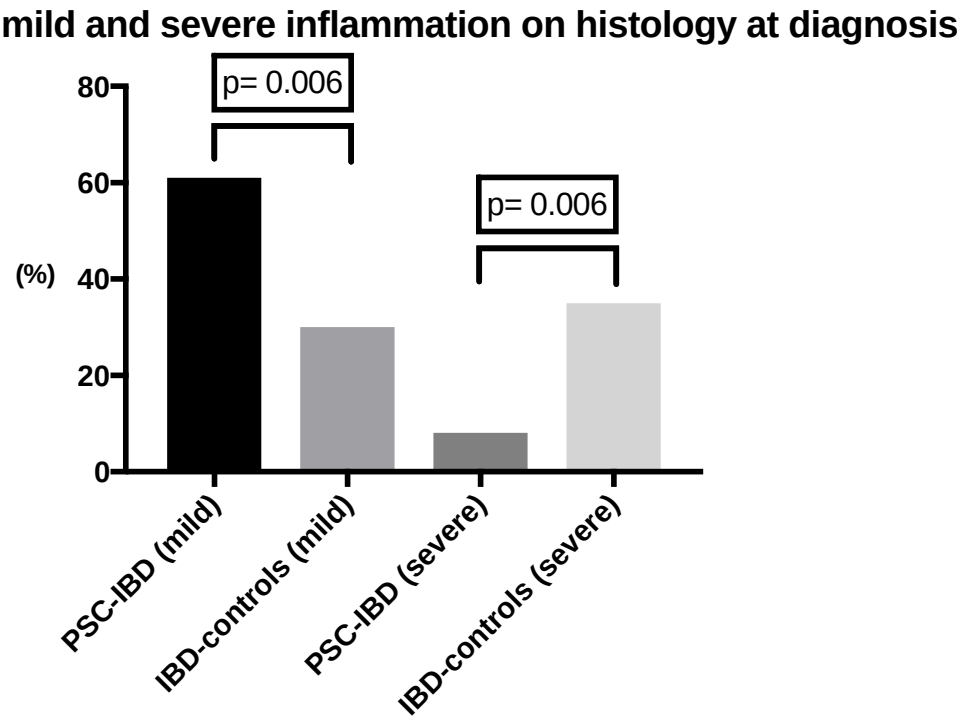
FIGURES

Figure 1. Rate of endoscopic remission and pancolitis (E4) at last follow-up in PSC-IBD cases and IBD-controls.



PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease, E4 = pancolitis

Figure 2. Rate of mild and severe inflammation on histology at diagnosis in PSC-IBD cases and IBD-controls.



PSC: primary sclerosing cholangitis, IBD: inflammatory bowel disease